

What is claimed is:

1. A biologically active conjugate of a biopolymer and a therapeutic agent comprising a compound of formula:



wherein A is a biopolymer, L is an optional spacer, B is a therapeutic agent, and each S is a sulfur atom.

2. The conjugate of claim 1, wherein the spacer is a lower normal or iso-substituted alkyl group.
3. The conjugate of claim 2, wherein the spacer is an ethyl group.
4. The conjugate of claim 1, wherein the spacer is absent.
5. The conjugate of claim 1, wherein the biopolymer is selected from the group consisting of hyaluronic acid, carboxymethyl cellulose, carboxymethyl amylose, carboxymethyl chitosan, chondroitin-6-sulfate, dermatin sulfate, polycarbophil, heparin, and heparin sulfate.
6. The conjugate of claim 5, wherein the biopolymer is hyaluronic acid.
7. The conjugate of claim 6, wherein the hyaluronic acid has a molecular weight in the range of from about  $7.5 \times 10^2$  daltons to about  $1 \times 10^7$  daltons.
8. The conjugate of claim 1, wherein the biopolymer is selected from the group consisting of polyacrylic acid, poly- $\alpha$ -glutamic acid, poly- $\gamma$ -glutamic acid, carrageenan, calcium alginate and sodium alginate.

9. The conjugate of claim 1, wherein the therapeutic agent is selected from the group consisting of small organic molecules, proteins, peptides, nucleic acids, antibodies, amino acids, lipids, polysaccharides, cell growth factors, and enzymes.
10. The conjugate of claim 9, wherein the therapeutic agent is a native or recombinant colony stimulating factor.
11. The conjugate of claim 9, wherein the therapeutic agent is an amino acid.
12. The conjugate of claim 9, wherein the therapeutic agent is glucocerebrosidase.
13. The conjugate of claim 1, wherein the biopolymer is linked to the remainder of the conjugate through one or more pendant carboxylic acid groups on the biopolymer backbone.
14. The conjugate of claim 1, wherein the biopolymer is linked to the remainder of the conjugate through a single carbonyl group on the terminal portion of the biopolymer.
15. A method for preparing a biologically active conjugate of a biopolymer and a therapeutic agent comprising a compound of formula:



wherein A is a biopolymer, L is an optional spacer, B is a therapeutic agent, and each S is a sulfur atom, said method comprising the steps of

selecting a biopolymer having specificity for a cell type, tissue type or organ in a subject,

reacting the biopolymer with an organic disulfide compound containing a spacer and a terminal group capable of reacting with the biopolymer,

selecting a therapeutic agent for a particular application for delivery to the desired *in vivo* target, said therapeutic compound containing a reactive thiol group,

reacting the modified therapeutic agent with the modified biopolymer to form a biologically active conjugate of formula A-L-S-S-B, and

isolating the biologically active conjugate.

16. The method of claim 15, wherein the biopolymer is selected from the group consisting of hyaluronic acid, carboxymethyl cellulose, carboxymethyl amylose, carboxymethyl chitosan, chondroitin-6-sulfate, dermatin sulfate, polycarbophil, heparin, and heparin sulfate.
17. The method of claim 16, wherein the biopolymer is hyaluronic acid.
18. The method of claim 17, wherein the hyaluronic acid has a molecular weight in the range of from about  $7.5 \times 10^2$  daltons to about  $1 \times 10^7$  daltons.
19. The method of claim 17, wherein the organic disulfide compound is 3-nitro-2-pyridinesulfenyl-ethylamine.
20. The method of claim 17, wherein the biopolymer is reacted with a carbodiimide prior to reaction with the organic disulfide compound.
21. The method of claim 16, wherein the biopolymer is activated by reaction with an activating agent prior to reaction with the organic disulfide compound.
22. The method of claim 21, wherein the biopolymer is linked to the remainder of the conjugate through one or more pendant carboxylic acid groups on the biopolymer backbone.
23. The method of claim 15, wherein the biopolymer is selected from the group consisting of polyacrylic acid, poly- $\alpha$ -glutamic acid, poly- $\gamma$ -glutamic acid, carrageenan, and sodium alginate.
24. The method of claim 15, wherein the therapeutic agent is selected from the group consisting of small organic molecules, proteins, peptides, nucleic acids, amino acids, antibodies, lipids, polysaccharides, cell growth factors, and enzymes.

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25. The method of claim 24, wherein the therapeutic agent is a native or recombinant colony stimulating factor.
26. The method of claim 24, wherein the therapeutic agent is an amino acid.
27. The method of claim 24, wherein the therapeutic agent is glucocerebrosidase.
28. The method of claim 15, wherein the biopolymer is linked to the remainder of the conjugate through a single carbonyl group on the terminal portion of the biopolymer.
29. A chemically modified biopolymer comprising the reaction product of a biopolymer, an activating agent, and an organic disulfide compound, said biopolymer containing at least one carboxylic acid group on the biopolymer backbone which reacts with an amino or hydroxyl group on the terminal portion of the organic disulfide compound..
30. The chemically modified biopolymer of claim 29, wherein the biopolymer is selected from the group consisting of hyaluronic acid, carboxymethyl cellulose, carboxymethyl amylose, carboxymethyl chitosan, chondroitin-6-sulfate, dermatin sulfate, polycarbophil, heparin, and heparin sulfate.
31. The chemically modified biopolymer of claim 30, wherein the biopolymer is hyaluronic acid.
32. The chemically modified biopolymer of claim 29, wherein the biopolymer is selected from the group consisting of polyacrylic acid, poly- $\alpha$ -glutamic acid, poly- $\gamma$ -glutamic acid, and alginate.
33. The chemically modified biopolymer of claim 29, wherein the organic compound is selected from the group consisting of nitro-pyridines, thio-pyridines, substituted S-phenyl disulfides, S-sulfonate derivatives, 9-anthrylmethyl thioesters, S-carboxymethyl derivatives and nitro-thiobenzoic acid derivatives.

34. The chemically modified biopolymer of claim 33, wherein the organic compound is a thio-nitro-pyridine.

35. The chemically modified biopolymer of claim 29 or 33 wherein the terminal group is an amino group.

36. The chemically modified biopolymer of claim 29 or 33 wherein the disulfide is linked to the terminal group with a lower normal or iso-substituted alkyl spacer.

37. A chemically modified biopolymer comprising the reaction product of a biopolymer, a reducing agent, and an organic disulfide compound, said biopolymer containing a carbonyl group on the terminal portion of the biopolymer which reacts with an amino or hydroxyl group on the terminal portion of the organic disulfide compound.

38. The chemically modified biopolymer of claim 37, wherein the biopolymer is selected from the group consisting of hyaluronic acid, carboxymethyl cellulose, carboxymethyl amylose, carboxymethyl chitosan, chondroitin-6-sulfate, dermatin sulfate, polycarbophil, heparin, and heparin sulfate.

39. The chemically modified biopolymer of claim 38, wherein the biopolymer is hyaluronic acid.

40. The chemically modified biopolymer of claim 37, wherein the biopolymer is selected from the group consisting of polyacrylic acid, poly- $\alpha$ -glutamic acid, poly- $\gamma$ -glutamic acid, and alginate.

41. The chemically modified biopolymer of claim 37, wherein the organic compound is selected from the group consisting of nitro-pyridines, thio-pyridines, substituted S-phenyl disulfides, S-sulfonate derivatives, 9-anthrylmethyl thioesters, S-carboxymethyl derivatives and nitro-thiobenzoic acid derivatives.

42. The chemically modified biopolymer of claim 41, wherein the organic compound is a thio-nitro-pyridine.

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43. The chemically modified biopolymer of claims 37 or 41 wherein the terminal group is an amino group.
44. The chemically modified biopolymer of claims 37 or 41 wherein the disulfide is linked to the terminal group with a lower normal or iso-substituted alkyl spacer.
45. A pharmaceutical composition comprising the conjugate of claim 1, and a pharmaceutically acceptable carrier.
46. The pharmaceutical composition of claim 45, wherein the biopolymer is selected to target cancer cells.
47. The pharmaceutical composition of claim 45, wherein the biopolymer is selected to target liver cells.
48. The pharmaceutical composition of claim 45, wherein the biopolymer is selected to target spleen cells.
49. The pharmaceutical composition of claim 45, wherein the therapeutic agent is native or recombinant colony stimulating factor.
50. The pharmaceutical composition of claim 45, which is formulated to provide sustained *in vivo* release of the biologically active conjugate.
51. A method for treating a subject comprising administering to the subject the pharmaceutical composition of claim 45.
52. The method of claim 51, wherein the pharmaceutical composition has enhanced *in vivo* stability in a subject.
53. The method of claim 51, wherein the pharmaceutical composition targets liver cells.

54. The method of claim 51, wherein the pharmaceutical composition targets cancer cells.

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